REMARKS

The status of the claims is as follows:

Original:	2-17
Currently amended:	1 and 20
Previously presented:	18 and 19
Canceled:	21-23
Withdrawn:	None

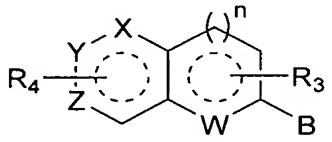
Claims 1-20 will be pending with entry of this amendment. Reconsideration is requested.

Part (v) of the definition of L in claim 1 has been removed, and the prevention language in claim 20 has been removed. Neither change introduces new matter.

Restriction Requirement

The assertion that the restriction requirement is proper and thus made final is acknowledged. The withdrawn subject matter has been removed from claim 1. Applicants reserve the right to pursue claims directed to the withdrawn subject matter in one or more continuing applications. It is also emphasized that the amendment to claim 1 is solely in response to the restriction requirement, and not to any of the substantive rejections in the office action.

Reconsideration of the finality of the restriction requirement is nonetheless requested. The Examiner has asserted that there is a lack of unity due to the disclosure of US 5945431 (referred to herein as "Jin"). Applicants disagree. Jin teaches a compound of formula:



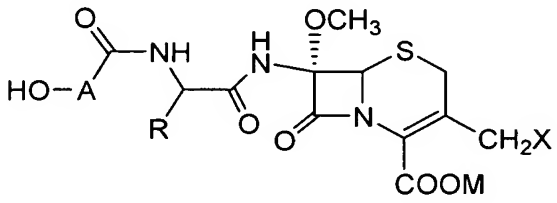
wherein each of W, X, Y, Z, B, R3, R4 and n can have any of several values. The compound genus accordingly embraces many thousands of compounds. Out of the myriad of compounds embraced by the genus, Jin directs the skilled reader toward 1,6-naphthyridines; i.e., the list of preferred embodiments in Jin are 1,6-naphthyridines (see col. 6, lines 16-25) and all of the specific compounds disclosed therein are 1,6-naphthyridines. The Examiner asserts Jin teaches an embodiment in which X and W are N; R3 and R4 are OH; B is C(=O)NR; and R is alkyl, aryl or heteroaryl. That is not correct. Nowhere does Jin disclose this particular combination of values for these variables. Instead the Examiner has selected this combination using the claimed compounds as a blueprint - this is pure and simple a hindsight reconstruction of the invention. Nothing in Jin would teach, suggest or motivate the person of ordinary skill in the art to select this specific combination of values. There are no blaze marks in the Jin patent that would lead the skilled artisan in this direction. Rather, Jin would lead the skilled artisan to 1,6-

naphthyridines. The only reference to 1,5-naphthyridines in Jin is concerned with suitable intermediates (col. 11, lines 33-35). This passing reference is insufficient to motivate the skilled artisan to pursue 1,5-naphthyridines, and, assuming arguendo that it did provide the motivation, it does not point to the claimed compounds which require a carboxamide substituent in the 3-position (whereas the Jin compounds require carboxamide in the 2-position) and which require an oxo substituent in the 2-position and an OH substituent in the 4-position (whereas Jin only discloses oxo and OH as alternatives in a set of many suitable moieties for several of the variables in the genus compound). In short, the claimed invention does have a significant structural element qualifying as a special technical feature that defines a contribution over the prior art. Accordingly, it is both incorrect and unreasonable to conclude that the Jin document destroys the unity of invention.

Rejection under 35 U.S.C. § 103

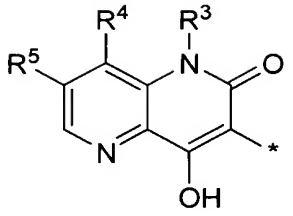
Claims 1-13 and 18 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over US 4125611 ("Yamade") and US 4226863 (divisional of the '611 patent). This rejection is traversed.

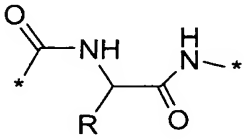
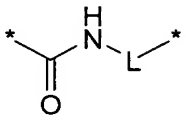
Yamade discloses compounds of formula I:

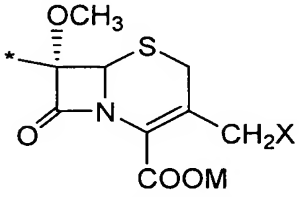
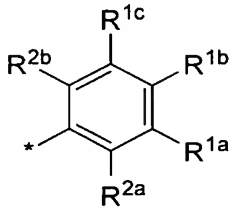


in which the cephem core is substituted at the 7 position by methoxy and by a substituted acetamide. In this formula, A is a mono- or polycyclic heteroaromatic ring containing at least one N and is unsubstituted or substituted with one or more substituents (see col. 1, lines 48-50). Yamade also discloses a list of 17 heteroaromatic rings exemplifying A, wherein the list includes naphthyridine (col. 2, lines 44-50). The document further provides several examples of specific compounds embraced by formula I in which A is a 1,5-naphthyridine. Presumably, the Examiner has relied on this disclosure to characterize Yamade as teaching "1,5-naphthyridine compounds of formula I" (see page 5, lines 7-8 of the Office Action). This is a mischaracterization of Yamade. Although A can be a naphthyridine, it can also be any of a large number of other heteroaromatic rings. The key moiety in the Yamade compound is the cephem core whose presence is required. Thus, the compounds of formula I are best characterized (as Yamade itself does) as cephalosporins, not naphthyridines.

The differences in the structures of the Yamade compounds and the claimed compounds are substantial. Most strikingly, the Yamade compounds require a cephem core, whereas the instantly claimed compounds exclude such moieties. More particularly, consider the moieties of the Yamade compounds and the corresponding moieties of the claimed compounds:

(1) HO-A-* in formula I of Yamade corresponds to  in the claimed compounds;

(2)  in formula I of Yamade corresponds to  in the claimed compounds; and

(3)  in formula I of Yamade corresponds to  in the instant claims.

Referring to (2), no value of L will provide a linking group that is at all similar to the Yamade linking moiety; i.e., L is a carbon chain, not an alkylcarbonylamino chain of formula -C(R)-C(=O)-NH- as required in Yamade. Referring to (3), the required cephem moiety in the Yamade compounds has no counterpart in the instant claims; i.e., the phenyl moiety in the claimed compounds is not even remotely similar. No overlap exists between the Yamade compounds and the claimed compounds, and nothing in Yamada even remotely suggests the claimed compounds. To the extent Yamade would motivate the person of ordinary skill in the art to modify the compounds disclosed therein, the modifications would be toward the development of new cephalosporins containing the cephem core. The claimed compounds are therefore not prima facie obvious in view of Yamade.

Withdrawal of the section 103 rejection is accordingly requested.

Rejection under 35 U.S.C. § 112

Claims 19 and 20 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserts that these claims fail "to comply with the written description requirement because the specification does not enable one skilled in the art to which it pertains ..." (Office Action, page 7, lines 12-13 from the bottom) The Examiner is reminded that written description and enablement are two separate requirements. It is not entirely clear whether these claims are being rejected for lack of written description or for lack of enablement or for both. However, the subsequent analysis in the Office Action focuses on the *In re Wands* factors which relate to

enablement, so it is assumed here that this rejection is an enablement rejection only. If this assumption is incorrect and the remarks which follow are deemed insufficient to overcome the instant rejection, it is requested that this rejection be withdrawn and a new, non-final office action be issued clearly stating the rejection and the reasons therefor.

This rejection is traversed with respect to claim 19 and claim 20 as amended herein. The amendment to claim 20 has removed the recitation directed to prevention. To the extent this rejection is based upon the prevention language in claim 20, it is moot. Applicants reserve the right to pursue claims directed to prevention in one or more continuing applications.

(Note: All documents referenced in the remarks below are cited in an accompanying IDS and copies thereof are enclosed with the IDS, except for Remington's Pharmaceutical Sciences.)

The rejected claims are directed to a method of inhibiting HIV integrase (claim 19) and a method of treating HIV infection, treating AIDS, or delaying the onset of AIDS (claim 20).

The specification provides sufficient disclosure to enable a person of ordinary skill in the art to make and use the invention as set forth in the rejected claims without undue experimentation. More particularly, the specification discloses that HIV is the etiological agent responsible for AIDS (page 1, lines 18-21), that integration of the proviral DNA into the host cell genome is a required step in HIV replication (page 1, lines 22-24), and that HIV integrase, the enzyme mediating the integration of the proviral DNA, is one of the enzymes that has been shown to be essential for the replication of HIV (the paragraph bridging pages 1-2). The person of ordinary skill in the art would also have had knowledge of LaFemina et al., *J. Virology* 1992, 66(12), pp. 7414-7419, which provides evidence that the integrase enzyme is required for the productive infection of human T-lymphoid cells.

The specification further discloses a group of novel hydroxynaphthyridinone carboxamides and embodiments and classes thereof (pages 3-40), and further discloses that the carboxamides are useful in the inhibition of HIV integrase, the treatment of infection by HIV, the treatment of AIDS and the delay in the onset of AIDS (page 3, lines 18-22; the paragraph bridging pages 46-47). The specification provides comprehensive guidance and directions on how to prepare these carboxamides via Schemes 1 to 5 (page 58, line 29 to page 65, line 18) and Examples 1 to 27. The specification further discloses that compounds representative of the claimed carboxamides have been shown by testing in suitable assays to inhibit HIV integrase (Example 29) and to inhibit the replication of HIV (Example 30).

The specification also discloses means for administering the claimed compounds (page 47, line 10 to page 48, line 19), provides guidance on the preparation of pharmaceutical compositions for administration of the compounds including a cite to the 18th edition of

Remington's Pharmaceutical Sciences (page 48, lines 20-27), and provides guidance on suitable dosage ranges for oral administration of the compounds (the paragraph bridging pages 48-49).

Applicants' position is that this disclosure is sufficient to enable the rejected claims. More particularly, using this description, optionally in combination with know-how available in the art, the person of ordinary skill can without undue experimentation prepare and administer a compound of the invention in a suitable carrier and in the appropriate dosage form and dosage amount to a subject in order to inhibit HIV integrase, treat HIV infection, treat AIDS, or delay the onset of AIDS.

The following are detailed remarks addressing specific issues raised by the Examiner in the Office Action:

1. The Examiner notes in the Office Action (page 9, line 15) that the pharmaceutical art generally is unpredictable and questions whether the assay data presented in the application is sufficient to support claims 19 and 20 (page 9, line 20 to page 10, line 2). The assay data is sufficient, particularly when considered with information known to the person of ordinary skill at the time the application was filed. First, the specification discloses that representative compounds of the invention exhibit inhibition of strand transfer activity in HIV integrase (Example 29) and inhibition of HIV replication (Example 30). Representative compounds of the invention include the compounds set forth in Examples 1-27, which were determined to have IC_{50} values less than 0.5 μM in the strand transfer assay and IC_{95} values less than 5 μM in the replication inhibition assay.

The compounds of Examples 1-27 are all N-benzyl-4-hydroxy-2-oxo-1,2-dihydro-1,5-naphthyridine-3-carboxamides having an assortment of substituents. All of the compounds embraced by the instant claims possess the same N-benzyl hydroxynaphthyridinone carboxamide core structure present in the compounds of Examples 1-27. The person of ordinary skill in the art at the time the application was filed would believe that this core structure is the basis for the integrase inhibition activity and HIV replication inhibition activity of these compounds and would accordingly understand that the activity exhibited by the compounds in Examples 1-27 can be expected for other compounds embraced by the instant claims. The activity of the compounds embraced by the claims would vary with the type and number of substituents attached to the core, but the skilled artisan would expect the claimed compounds to share the same physiological activity as the compounds of Examples 1-27.

It is further noted that the strand transfer assay described in Example 29 does indeed identify true HIV integrase inhibitors. Reference is made to Hazuda et al., "Inhibitors of Strand Transfer That Prevent Integration and Inhibit HIV-1 Replication in Cells", *Science*, 287, pp. 646-650 (January 2000). Hazuda et al. note that integration involves three steps: (i) assembly of a stable preintegration complex, (ii) 3' processing, and (iii) strand transfer, wherein assembly is a

prerequisite for catalysis. Hazuda et al. further note that some compounds may appear to inhibit 3' processing and strand transfer but have no effect on either step when assayed subsequent to assembly; i.e., the compounds are not true integrase inhibitors. In order to identify inhibitors of integrase catalysis, Hazuda et al. disclose that they "biased the strand transfer reaction by means of preassembling recombinant integrase on immobilized oligonucleotides as a surrogate for preintegration complexes." (see p. 646 of Hazuda et al.) Using this strand transfer assay Hazuda et al. identified a series of diketo acid compounds that inhibit the strand transfer reaction and for the most potent analogs inhibit HIV-1 replication in cell culture. Hazuda et al. then employed two of the more active diketo acids in several experiments validating integrase as the molecular target. For example, Hazuda et al. found that variants of wild type HIV-1 resistant to the diketo acids contained mutations in the integrase coding region of their cDNA (see p. 647). Hazuda et al. also determined that the diketo acids affect integration activity without affecting synthesis or 3' processing of the viral DNA (see p. 648). Hazuda et al. also found that in cells acutely infected with wild-type HIV-1, the presence of a diketo acid resulted in the accumulation of integration-incompetent circular viral DNA products and a decrease of integration-competent linear viral DNA products (see p. 649).

The person of ordinary skill in the art would understand from reading Hazuda et al. that substances exhibiting inhibition activity in the assay disclosed therein (i.e., a strand transfer assay using preassembled integrase strand transfer complexes) are HIV integrase inhibitors. The assay employed to measure the integrase inhibition activity of the instantly claimed compounds (i.e., the assay described in Example 29 of the subject application) is a strand transfer assay using preassembled complexes of the type described by Hazuda et al. Accordingly, the person of ordinary skill in the art reading Example 29 in view of Hazuda et al. would understand that the compounds referred to in claim 19 are true HIV integrase inhibitors and thus would be effective in inhibiting HIV integrase.

It is still further noted that sufficient correlation between the HIV replication inhibition assay set forth in Example 30 and *in vivo* efficacy was established prior to the filing of the instant application. For example, indinavir sulfate (available as CRIXIVAN®, Merck & Co.) and efavirenz (available as SUSTIVA® in the U.S., Bristol-Myers Squibb) were approved by the FDA for the treatment of HIV infection prior to the filing of this application. During the early development of these HIV antivirals, both were tested in *in vitro* assays similar or identical to the HIV inhibition assay disclosed in the instant specification and both were found to be active. See, for example, US5519021, col. 31 (assay descriptions and results for efavirenz); S. D. Young et al., *Antimicrobial Agents & Chemotherapy* 1995, 39 (12): 2602-2605 (assay descriptions and results for efavirenz); US5413999, col. 58 (assay descriptions and results for indinavir); and J. P. Vacca et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096-4100 (assay descriptions and results for indinavir.) The person of ordinary skill in the art at the time of filing would have been aware of this correlation and would have expected a similar correlation with the claimed compounds.

2. The Examiner has asserted that undue experimentation would be necessary to determine which patients would benefit from treatment using one of the claimed compounds (Office Action, p. 10, lines 18-20). Applicants disagree. Given the discussion in Item 1 above, the person of ordinary skill in the art would understand that the claimed compounds are HIV integrase inhibitors that will inhibit HIV integrase and HIV replication upon contact with the virus. The person of ordinary skill in the art would also understand that, because the claimed compounds will inhibit HIV replication, there is a reasonable expectation that they will be effective in the treatment of HIV infection.

The skilled artisan would also reasonably expect the compounds to be effective in delaying the onset of AIDS and in treating AIDS. It was known prior to the filing of the instant application that infection by HIV can result in the progressive destruction of the immune system, specifically the depletion of CD4-positive T lymphocytes, resulting in acquired immune deficiency syndrome (AIDS) (Fauci et al., Ann. Int. Med., 100, 92-106 (1984); see also page 1, lines 18-21 of the subject application). It was also known that increases in HIV viral load are correlated to AIDS progression, and thus limiting the spread of the HIV virus will limit the viral load and postpone the onset of AIDS (Dean et al., Science, 273, 1856-62 (1996)). In other words, AIDS and the diseases and conditions associated with AIDS are due directly or indirectly to a compromised immune system which is the result of significant and/or prolonged HIV infection. Administration of appropriate HIV antiviral agents such as the claimed compounds can reduce the viral load to such a level that the onset of AIDS can be delayed or the progression of AIDS ameliorated or even reversed.

It is further noted that there is nothing unusual or difficult in the practicing the methods recited in claims 19 and 20; i.e., the compounds are administered to an individual in need of inhibition of HIV integrase, treatment of HIV infection, treatment of AIDS, or delay in the onset of AIDS. Identification of individuals infected by HIV and thus in need of treatment was without question well known in the art before the filing date of this application; i.e., numerous tests were available for diagnosis of HIV infection. See, for example, Mylonakis et al., *Am. J. Med.* November 2000, 109, pp. 568-576; *Med. Lett. Drugs Ther.* 1997, 39 (1008), pp. 81-83; and Constantine, *AIDS* 1993, 7, pp. 1-13. Furthermore, plasma viral load and CD4+ lymphocyte count were well established as prognostic markers for HIV. See, for example, Mellors et al., *Annals of Internal Medicine* 1997, 126 (12), pp. 946-954. Inhibition of HIV integrase, treatment of HIV infection or AIDS, and delay in the onset of AIDS are produced in the patient by bringing the HIV-infected cells into contact with an effective amount of the claimed compound. Modes of administration for achieving such contact and dose ranges suitable for administration are described in the specification. The person of ordinary skill in the art can apply this disclosure in combination with his general knowledge of the pharmaceutical art to administer the claimed compound in an amount effective for the inhibition of integrase, treatment of HIV infection or AIDS, or delay in the onset of AIDS.

It is admitted that, at the time the application was filed, none of the claimed compounds had been tested for safety and effectiveness in humans and thus *in vivo* efficacy had not been absolutely established. However, as indicated in the *Brana* decision, such testing is not required to establish utility under the patent law:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating the incentive to pursue, through research and development, potential cures in many crucial areas... *In re Brana*, 34 USPQ.2d 1436, 1442-3 (Fed. Cir. 1995).

The issue addressed in *Brana* concerned the utility of compound claims, not method claims such as those at issue here. However, Applicants' position is that *Brana* applies to method claims as well in that the showing required to establish patent utility for such claims "necessarily includes the expectation of further research and development."

In view of the foregoing remarks and the amendments to the claims, withdrawal of the section 112 rejection of claims 19 and 20 is requested.

Objections

Claims 14-17 have been objected to as being dependent upon a rejected base claim. The Examiner's invitation to rewrite claims 14-17 in independent form is declined, because in view of the claim amendments and accompanying remarks set forth above all of the pending claims are believed to be in condition for allowance. The Examiner is asked to telephone the undersigned should any minor matters need to be resolved before a Notice of Allowance can be mailed.

Respectfully submitted,

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